

Mechanisms of Toxicity/Carcinogenicity and Superfund Decisions

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Heavy metals that contaminate soils and water usually exist in various oxidation states and form a number of compounds with different physical and chemical characteristics. These differences are often reflected in dramatic variation in toxicokinetic and biologic properties. Such variation in properties, critical in determining intrinsic toxicity, often causes a great deal of uncertainty in analyses of public health risks at sites where metal exposure is evaluated. In the Superfund program, such uncertainties may substantially undermine attempts to characterize potential impacts to populations exposed to metals from improperly disposed waste. In the case of chromium, risk assessment uncertainties can be considerable and fall generally into two categories. First, there is almost no information on potential health effects due to chronic oral exposure to chromium-containing compounds, and a nonquantifiable and probably large uncertainty exists in establishing no-effect levels. In fact, reference doses (RfDs) for Cr^{II} and Cr^{VI} are based on chronic studies in which no adverse effects were seen even at the highest dose. Considerations of bioavailability, deduced from site characterization data, and acute toxicity indicate that general application of these RfDs may lead to highly inaccurate estimations of risk. Second, because of the ready reduction of Cr^{VI} in biological systems, it has not been possible to separate effects of Cr^{VI} from those of Cr^{III} . Thus, data on the relative toxicity and carcinogenicity of these two species is sparse and difficult to interpret. Moreover, kinetic considerations make it difficult to determine the site and rates of reduction of Cr^{VI} . This makes prediction of target site concentrations of the two species difficult. The problem is particularly acute following inhalation exposure, since epidemiologic studies suggest that chromium induces lung cancer by this route, yet animal studies show cancer induction at sites of injection in various tissues. Knowledge of mechanisms of toxicity and carcinogenesis, along with a more complete empirical database, would increase confidence in oral RfDs, assist in establishing inhalation RfDs, and help evaluate the overall impact of inhalation of chromium on the induction of cancer.

Introduction

Risk assessment activities at hazardous waste sites that have been placed on the National Priorities List (Superfund sites) involve both assessment of current and potential exposures related to contaminants at the site and an evaluation of the relationship between exposure to these contaminants and possible adverse health effects. Confidence in the latter evaluation is often dependent on the quality and quantity of experimental evidence for toxic effects of a contaminant when specified doses are administered to laboratory animals. Low confidence in these dose-response relationships implies a great deal of uncertainty in quantitative estimates of risk. Since uncertainties often are contentious in interactions among the public, potentially responsible parties, and EPA, efforts to reduce uncertainties in risk assessments should be given high priority.

In the case of chromium, dose-response relationships are relatively poorly defined, and this is the source of considerable uncertainty in quantitation of risks due to chromium exposure. Several problem areas, particularly those involving carcinogenic mechanisms, were extensively examined by other investigators during this symposium and will not be considered in this discussion. Instead, the focus of this presentation will be dose-response relationships involving noncarcinogenic end points. For such end points, EPA generally considers the reference dose (RfD) to be the appropriate critical toxicity value for purposes of risk assessment. The RfD is intended to represent that amount of a substance that can be consumed daily for a significant portion of a lifetime without inducing adverse health effects. For chromium, RfDs have been established for "insoluble" compounds where chromium is found in the +3 valence state and for "soluble" compounds where chromium is found in the +6 valence state. Generally, EPA considers a daily intake, estimated as part of an exposure assessment, that exceeds the RfD as posing the poten-

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tial for induction of adverse effects in at least a portion of the exposed population. Whether the RfD accurately reflects the actual potential of a compound to produce toxicity is dependent at least in part on how accurately experimental studies measure the dose-response relationship.

Oral RfD for Insoluble Chromium(III) Compounds

The RfD for insoluble Cr^{III} compounds, as described in EPA's Integrated Risk Information Service (IRIS) (1), is provided in Table 1. It is worthwhile to note that the RfD is based on a single study in which there are no toxic effects seen at any dose. The only way to derive an RfD from this study is to assume that the highest dose approximates a no-observable-adverse-effect level (NOAEL) and to apply safety factors to arrive at an RfD for humans. Recently, a site with the potential for exposure to chromium in contaminated soil has provided an opportunity to consider the soundness of this assumption.

At the site in question, both Cr^{III}, primarily as enriched chromite ore, and Cr^{VI}, primarily as soluble chromate salts, were present from uncontrolled releases from a chromate production process. In particular, there is, on-site, a large pile of chromite ore which has been used as a sandbox by neighborhood children in the past. Thus, one exposure scenario used in evaluating risk on the site involved the incidental ingestion of chromium in the ore during trespassing events by children. Because chromite is highly insoluble in water, it seemed reasonable to use the RfD for insoluble Cr^{III} compounds in quantifying risk. However, when the chromite ore was sampled and analyzed for total chromium, the concentration was found to be only 16 mg/kg. Since chromite ore is a concentrate ready for use in dichromate pro-

duction, the expected concentration of chromium would be between 25 and 40% or 25,000 to 40,000 mg/kg. Thus, the Contract Laboratory Procedures method, using a digestion in hot concentrated nitric acid, apparently solubilized only a small fraction of the total chromium (U.S. EPA, unpublished report). If a similar small fraction were solubilized in the digestive tract after ingestion, and 2% of the soluble Cr^{III} were absorbed (2), ingestion at the RfD rate would correspond to an absorbed dose of Cr^{III} of a few nanograms per kilogram per day. Even highly toxic metals such as lead are not measurably toxic at such low doses. In fact, the average daily absorbed dose of lead from dietary sources is estimated to be about 325 ng/kg/day for a 6-year-old child (3). Faced with these data, one must ask if the current RfD for insoluble Cr^{III} compounds is appropriate for chromite ore and perhaps other insoluble Cr^{III} forms. Clearly, additional chronic studies are needed to adequately define the chronic oral toxicity, if any, of the commonly encountered Cr^{III} compounds.

Oral RfD for Soluble Chromium(VI) Compounds

The IRIS entry for soluble Cr^{VI} compounds is provided in Table 2. As with Cr^{III}, the RfD is based on a study in which no adverse effects were seen, even at the highest administered dose. In this study, Cr^{VI} was added to drinking water in concentrations up to 25 ppm. It is interesting to note that this is five times the concentration of Cr^{VI} in water that produced nausea in a single volunteer. This volunteer used chromate-containing water in place of normal drinking water for a single day (4). This is by no means a definitive study, but it does suggest the possibility that toxicity following ingestion of chromate may occur only at levels of exposure that cause some acute symptoms. Again,

Table 1. Oral RfD summary for soluble Cr^{VI} compounds (6).

Study type	Critical effect	Experimental doses ^a	Uncertainty factor	Modifying factor	RfD
Rat chronic feeding study	No effects observed	NOEL: 5% ²⁵³ Cr in diet 5 days/week for 600 feedings (1800 g/kg body weight average total dose)	100	10	1E+0 mg/kg/day (as an insoluble salt)
LOAEL: none					

^aDose conversion factors and assumptions: 1800 g ²⁵³Cr/kg bodyweight × 1000 mg/g × 0.6849 Cr/g ²⁵³Cr/600 feeding days × 5 feeding days/7 days = 1468 mg/kg/day.

Table 2. Oral RfD summary for insoluble Cr^{III} compounds (7).

Study type	Critical effect	Experimental doses ^a	Uncertainty factor	Modifying factor	RfD
Rat 1-year, drinking study	No effects reported	NOAEL: 25 mg/L of chromium as K ₂ CrO ₄ (converted to 2.4 mg of Cr ^{VI} /kg/day)	500	1	5 × 10 ⁻³ mg/kg/day
LOAEL: none					

^aDose conversion factors and assumptions: drinking water consumption = 0.097 L/kg/day (reported).

chronic toxicity studies are needed in which doses are sufficiently high to produce some adverse effects. Such studies might need to address the potential problem of nausea by using animals that are able to regurgitate.

Pharmacokinetics of Chromium(VI)

Cr^{VI} is clearly reduced to Cr^{III} in the body. In theory, this reduction could profoundly affect the delivered dose of chromium in either valence state to sites for toxic action. For example, given IP, Cr^{III} causes extensive damage to the kidney (2). Slightly higher doses of Cr^{VI} cause a similar effect, but most of the chromium recovered in the urine is in the form of Cr^{III} . The inference is that Cr^{VI} is rapidly reduced in experimental animals and that Cr^{III} is responsible for the toxicity seen. It follows that, if substantial differences exist in the ability of humans and animals to reduce Cr^{VI} , or if there is substantial individual variation in the ability of humans to reduce Cr^{VI} , there will be considerable difficulty in extrapolating animal results to humans or in interpreting human epidemiological studies.

Some evidence that such differences may exist is provided by Korallus (5). In his paper, clear differences in distribution and excretion of chromium were found in workers occupationally exposed via inhalation to Cr^{VI} . In fact, the data suggest two distinct populations, perhaps genetically based, exist in the study populations (Fig. 1). One group apparently reduced Cr^{VI} rapidly, and large amounts of Cr^{III} were excreted in the urine. The other group apparently reduced Cr^{VI} more slowly and excreted less Cr^{III} . Differences in reducing capacity were thought to be based extracellularly in the blood. Apparently, this finding has not yet been duplicated in other worker populations or by other investigators. Nevertheless, the study at least raises the question of how differences in the ability to reduce Cr^{VI} might influence

toxicity. For example, one might imagine that rapid reduction of Cr^{VI} in the blood would produce relatively high concentrations of Cr^{III} . After filtration at the glomerulus, this Cr^{III} might concentrate in the urine, delivering a higher dose of the toxic chromium form to the kidney tubules.

On the other hand, slow reduction of Cr^{VI} in the blood could allow the Cr^{VI} to penetrate into cells. Once there, reduction would produce Cr^{III} intracellularly. Since Cr^{III} crosses membranes very poorly (2), reduction would effectively trap the chromium inside of cells. Cells susceptible to the carcinogenic actions of chromium (or other adverse effects) might thus receive a higher dose in individuals that reduced Cr^{VI} slowly in the blood. Such individuals might be less susceptible to kidney damage because of lower blood Cr^{III} levels. However, tissue Cr^{III} levels might be higher, making slow reducers susceptible to other toxic effects, including cancer.

Finally, if the ability of blood to reduce chromate is saturable in the range of doses that might be expected in human exposures, there may be differences in expected toxicity when the dose absorbed exceeds the reducing capacity of the blood. That is, doses that saturate the reduction capacity of the blood would be expected to increase tissue chromium levels regardless of an individual's reducing capacity. Thus, at high doses, the concentration of chromium at target sites may be better predicted by administered or exposed dose.

In any event, it seems clear that studies on the pharmacokinetics of chromium need to be carried out. Such studies should include both human exposures and the use of experimental animals and should focus on estimating dose delivered to specific target sites, such as the kidney. In addition, more information is needed to define the variation in blood-reducing capacity in the human population studies.

Summary

In summary, available data on chromium make risk assessments using EPA critical toxicity values (RfDs) very uncertain. The basic problem lies in our current inability to confidently predict the dose of chromium that actually reaches its site of toxic action in the body. Examination of the RfD for insoluble Cr^{III} compound suggests that the RfD could overestimate risks by at least a few orders of magnitude for some Cr^{III} compounds. Similar consideration of the RfD for soluble Cr^{VI} compounds reveals the possibility that toxicity might occur only at doses high enough to cause acute symptoms, such as nausea. Finally, the pharmacokinetics of Cr^{VI} after absorption may be complex and variable in the human population. This suggests that there could be human subgroups with greater sensitivity to some of the potential toxic effects of chromium. It seems clear that risk assessments based on exposure to chromium compounds could be improved dramatically with increased attention among researchers to the kinetics of chromium in mammalian systems.

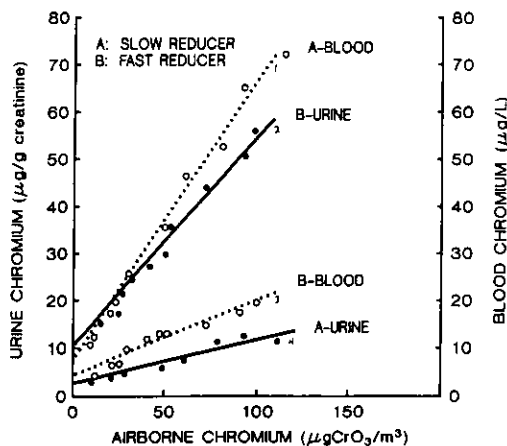


FIGURE 1. Linear relationship between the airborne hydrosoluble chromium concentration and the chromium concentration in blood and urine at the end of a 5-day shift in workers at a dichromate plant. From Korallus (5).

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